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THE EFFECT OF CAFFEINE ON ENDURANCE TIME TO EXHAUSTION AT HIGH ALTITUDE

U S ARMY RESEARCH INSTITUTE
OF
ENVIRONMENTAL MEDICINE
Natick, Massachusetts

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Endurance time to exhaustion (ETX) is increased at high altitude (HA) but only after 2 weeks of continued exposure. The increase is thought to be related to a delayed depletion of muscle glycogen, secondary to HA-induced increases in the mobilization and utilization of free fatty acids (FFA). This study determined if caffeine (CAF), which stimulates FFA mobilization, could prolong ETX earlier in the HA exposure. Eight untrained men (17 to 24 yr) performed 2 ETX cycling bouts at 79% to 85% of their altitude-specific maximal oxygen consumption in each of 3 phases: at sea level (SL), after 1 h simulated exposure (acute), and after 2 weeks (chronic) at 4300 m. Subjects received either a CAF (4 mg/kg) or a placebo drink in a double-blind cross-over design 1 h prior to each ETX bout in each phase. Subjective ratings of perceived exertion (PE) and cardiac output (CO) were obtained during exercise. Daily caloric intake and composition were held constant. CAF did not alter ETX at SL but was increased by 54% (22.0 to 35.0 min,p=.04) and 24% (30.8 to 38.5 min, p=0.11) during acute and chronic HA exposure, respectively. The improvements in ETX were determined

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THE EFFECT OF CAFFEINE ON ENDURANCE TIME TO EXHAUSTION AT HIGH ALTITUDE

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DISCLAIMER

Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of Volunteers in Research.

The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

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ABSTRACT:

Endurance time to exhaustion (ETX) is increased at high altitude (HA) but only after 2 weeks of continued residence. The increase is thought to be related to a delayed depletion of muscle glycogen, secondary to HA-induced increases in the mobilization and utilization of free fatty acids (FFA). This study determined if caffeine (CAF), which stimulates FFA mobilization, could prolong ETX earlier in the HA exposure. Eight untrained men (17 to 24 yr) performed 2 ETX cycling bouts at 79 to 85% of their altitude-specific maximal oxygen uptake in each of 3 phases: at sea level (SL), after 1 h simulated exposure (acute), and after 2 weeks (chronic) at 4300 m. Subjects received either a CAF (4 mg/kg) or a placebo drink in a double-blind cross-over design 1 h prior to each ETX bout in each phase. Subjective ratings of perceived exertion (PE) and cardiac output (CO) were obtained during exercise. Daily caloric intake and composition were held constant. CAF did not alter ETX at SL but was increased by 54% (22.0 to 35.0 min, $p<0.05$) and 24% (30.8 to 38.5 min, $p<0.11$) during acute and chronic HA exposure, respectively. The improvements in ETX were determined not to be associated with substrate mobilization and utilization, or to a reduction in PE. Dietary or CO changes also could not account for the improvements. However, increases in tidal volume during CAF treatment suggest that the improvements in ETX at HA may be related to an observed increase in tidal volume which increases the partial pressure of alveolar O_2 and enhances arterial saturation and oxygen transport.

INTRODUCTION:

The current Army TB MED 288 indicates that the maximal oxygen uptake (VO_{2max}) of a soldier is diminished immediately upon arrival at altitudes greater than 1500 meters and is inversely related to the final elevation obtained (21). For example, at 4300 meters VO_{2max} is approximately 75% of the value obtained at sea level (12,13) and will be reduced to this level for as long as the soldier remains at this altitude (26). Although VO_{2max} is measured during maximal effort of a relatively brief duration, the decrease in VO_{2max} at high altitude also is reflected in more prolonged exercise of less severe intensity (11).

Oxygen uptake at any fixed exercise intensity up to maximal levels at altitude does not differ from sea level (12). However, because VO_{2max} is reduced at altitude, the oxygen uptake elicited by the fixed exercise intensity actually represents a greater fraction of VO_{2max} at altitude than it does at sea level (12). Therefore, the relative stress on the body will be greater to a degree that is proportional to the altitude-induced reduction in VO_{2max}. Thus, a soldier's endurance time for performing submaximal exercise at a fixed exercise intensity to exhaustion will be reduced at altitude.

Alternatively, if the exercise intensity is reduced so that the associated oxygen uptake elicits the same percentage of VO_{2max} during an acute altitude exposure as it does at sea level, endurance time to exhaustion will be similar between the two environments (13,17). With continued residence at altitude, the time to exhaustion is lengthened (17). The increase in endurance time without an associated increase in VO_{2max} can be related to a decreased anaerobic demand and rate of glycolysis during exercise, or increased mobilization and use of free fatty acids resulting in delayed depletion of muscle glycogen. Recent evidence suggests the latter. Young et al. (25) showed

that chronic altitude exposure (18 days) resulted in increased mobilization and utilization of free fatty acids (FFA) during submaximal exercise with an associated sparing of muscle glycogen. However, since the exercise bouts were limited to 30 minutes in this study, the actual benefit, in terms of performance time, of the metabolic shift towards a greater dependence on FFA could not be assessed.

While an increase in submaximal endurance time has been observed repeatedly at altitude, a significant increase from sea level does not occur until after about 2 weeks of residence (13,17). Any factor which would prolong endurance time sooner than two weeks or prolong endurance at any time during a sojourn would be beneficial, especially for military operations. Caffeine may be that factor. Caffeine stimulates the mobilization of FFA and has been shown to increase the rate of lipolysis which is thought to reduce the rate of glycogen depletion from the liver and skeletal muscle which, in turn, could prolong endurance exercise (2,7,8). At sea level, there is considerable evidence that caffeine enhances performance in submaximal long-term exercise although the exact mechanism remains elusive (5,9,14,19). In addition to the effect of caffeine on FFA mobilization and utilization, caffeine also causes a reduction in the perception of effort (3,8,19) and an increase in muscular tension development (16). Caffeine also has a ventilatory effect which may aid endurance performance particularly at altitude By increasing alveolar ventilation and the partial pressure of alveolar O_2, the gradient from the lung to the capillary is increased allowing an increased arterial oxygen saturation and an improved O_2 transport (15,19,20).

The primary objective of this study was to determine if caffeine could prolong endurance time to exhaustion during the acute and chronic stages of acclimatization.

I. METHODS:

Eight healthy male soldiers who had been participating in the usual Army physical training volunteered for this study. Each gave informed consent and all were highly motivated. Each subject underwent a medical history and a physical examination and none was found to have any contraindications to altitude exposure or caffeine. Ages ranged from 17 to 24 years (mean:20.8), heights from 140.0 to 176.4 cm (mean:165.1), and weight from 63.5 to 86.9 kg (mean:74.4). All were life long sea-level residents who had not been exposed to altitudes greater than 1500 meters for at least six months before the study began.

The study was conducted over the course of nine weeks both in the hypobaric environmental chamber at the United States Army Research Institute of Environmental Medicine in Natick, MA (50 m, P_IO_2=159 Torr), and at the U.S. Army Pikes Peak Laboratory on the summit of Pikes Peak, Colorado (4300 m, P_IO_2=94 Torr). To become familiarized and habituated with the tasks, equipment, personnal, and procedures, the subjects were required to practice pedalling several times on a cycle ergometer in the chamber (P_IO_2=159 Torr) during the first week of the study. Maximal and submaximal oxygen uptake tests were performed during three phases: at sea level, during one-hour hypobaric exposures (4300 m equivalent), and at Pikes Peak.

Maximal oxygen uptake (VO_{2max}) was determined on five separate occasions: twice at sea level during weeks two and three of the study, once at 4300 m simulated altitude (1-h hypobaric exposure) during week four, and twice at Pikes Peak at the end of weeks seven and eight (the first and second weeks of the sojourn). A continuous, incremental cycling protocol on an electrically-braked Collins ergometer was employed (Collins, Inc). The subjects, paced by a metronome, pedalled at a frequency of 60 rpm. The

subjects started at 25 watts for two minutes followed by an incremental increase of 25 watts every two minutes until VO_{2max} was obtained or until the subject could no longer continue.

Submaximal endurance tests were performed a total of six times: twice at sea level during week three of the study, twice in the altitude chamber (1-h hypobaric exposure) during week four, and twice at Pikes Peak during week nine (the third week of the altitude sojourn). There were three days of rest between the two submaximal endurance tests in each phase. There were also four days of rest between the VO_{2max} test and the first submaximal endurance test in each phase. The exercise intensity of the ergometer was started at 50 watts and was gradually increased (over 30 seconds) until the subjects were pedalling against an exercise intensity calculated to elicit 80 to 85% of their VO_{2max} measured in each phase. Minor changes in exercise intensity were made during the first five minutes based on VO_2 values with no further adjustment in exercise intensity thereafter.

Ratings of perceived exertion were obtained from the exercising subjects during the submaximal endurance tests using the Borg scale (4): a 15-point continuous scale from 6 to 20 with each odd number anchored by a verbal expression of difficulty ranging from "very, very light" to "very, very hard". Every fifth minute, subjects were asked to provide ratings of exertion by pointing to a large placard placed near the ergometer. The subjects rated the subjective feelings they had of the present exercise intensity in each of three areas: their exercising muscles ("local"), their respiratory and cardiovascular systems ("central"), and their "overall" feeling of exertion (4,24). The subjects continued pedalling at a rate of 60 rpm until they could no longer continue despite strong verbal encouragement. Total time to exhaustion was recorded. Emphasis was placed on leg fatigue and not leg pain as the end point.

Two days prior to the first endurance test through the day of the second endurance test in each phase (a total of 6 days), the subjects consumed a mixed, caffeine-free diet consisting of 3600 Kcal/day (50% CHO, 15% PRO, 35% FAT). All meals and snacks were prepared by registered dietitions and were balanced nutritionally. The daily sequence and composition of meals were identical between phases. On the days of the submaximal endurance tests, each subject completed either breakfast or lunch two hours prior to the initiation of testing.

Four subjects were randomly chosen to consume a seven-ounce caffeine drink one hour prior to the first endurance test of the sea-level phase. The remaining four consumed an identically-appearing and tasting placebo. Three days later, each subject received the opposite therapy. The placebo consisted of approximately 250 ml of water, decaffeinated tea, and Sweet and Low (Parve Co.). The caffeine drink was a mixture of the placebo, Equal (G.D. Searle & Co.), and anhydrous caffeine (4 mg/kg body weight; Sigma Co.). The drinks were made and distributed throughout the study by an investigator noninvolved with the testing. The subjects were required to finish the drink in 30 seconds or less. Neither the subjects nor the investigators involved with the testing knew the contents of the drinks. The day-to-day sequence of subjects receiving caffeine or placebo within each phase did not vary between phases.

A Sensormedics Metabolic Measurement Cart Horizon System (MMC; Sensormedics Corp.) was used to collect respiratory metabolic data during the maximal and submaximal tests. The MMC was calibrated with medical grade calibration gases prior to each test. Expired air was channeled from a low resistance valve and tubing into a mixing chamber within the MMC. For each minute, mixed expired gas was sampled from the mixing chamber for 45 seconds alternated with 15 seconds of sampling end-tidal values for oxygen and carbon dioxide directly from the mouthpiece. A mean for each value for the 15-second

period was determined. Analog heart rate signals from a heart rate monitor (IBS, Inc) were continuously fed to the MMC. Values for heart rate, minute ventilation, oxygen consumption, carbon dioxide production, and respiratory exercise ratio were calculated and printed every 15 seconds. A minute-to-minute summary report which averaged the four 15-second periods of each minute was printed at the conclusion of each test and was subsequently used to provide the information for analysis of the respiratory data. During the submaximal endurance tests, the MMC was used also to calculate cardiac output approximately every 10 to 15 minutes using a CO_2-rebreathing method as described in the handbook accompanying the MMC.

Prior to each submaximal endurance test, each subject had an indwelling catheter placed into a superficial vein of the forearm. A 7-ml blood sample was withdrawn at rest, at minute 10, and at exhaustion to assess energy substrate metabolism during exercise with and without caffeine. Each sample was immediately divided into aliquots to be centifuged, frozen, or analyzed. Measured were glucose, lactate, glycerol, free fatty acids, Hct, and Hb.

Data were analyzed using a three-way ANOVA with repeated-measures. The main factors were time at altitude, exercise time, and treatment (placebo vs. caffeine). When a statistically significant F-ratio was calculated, differences between the means were tested for significance using Tukey's post-hoc test. The level of significance was chosen as $p<0.05$.

II. RESULTS:

Maximal Oxygen Uptake

There were no significant differences between the two sea-level determinations of VO_{2max} (mean $\pm$ SE, 3698 $\pm$ 245 vs 3748 $\pm$ 218 ml/min). Therefore, the latter determinations were designated as the sea-level baseline values and were used in calculating the sea level submaximal exercise intensities. Maximal oxygen uptakes decreased by 26.6% to 2751 $\pm$ 124 ml/min during the acute (1 hr) chamber exposure, and by 25.1% (2807 $\pm$ 135 ml/min) and by 22.5% (2906 $\pm$ 138 ml/min) during the first and second weeks of the sojourn at Pikes Peak (chronic phase). There were no significant differences between the acute and chronic VO_{2max} values or between the two sets of determinations at Pikes Peak. The VO_{2max} values measured in the second week at Pikes Peak were used in calculating the exercise intensities of the submaximal endurance tests during the third week of the exposure.

Endurance Times to Exhaustion

The endurance times to exhaustion varied considerably from individual to individual despite the exercise intensities between the subjects being within a very narrow range throughout the entire study. The individual endurance times ranged from less than 12 minutes to more than 68 minutes while the mean exercise intensities ranged from 79.1% to 85.2% of the altitude-specific VO_{2max}. Furthermore, the difference in mean exercise intensities within each of the three phases never exceeded 1.2% between the placebo and caffeine therapies (Figure 1). Because of the short endurance times of some of the subjects, the only exercise and blood data being reported prior to exhaustion had to be limited to that collected during the 10th minute. Reporting the

data using this point in time (an amount of time that all of the subjects were able to obtain in all phases), obviated the statistical analysis problems associated with missing values in the current, repeated-measures designed study.

Since the primary objective of this investigation was to determine if caffeine could enhance performance during the acute and chronic phases at altitude and not in the physiological changes that occur in the transition from sea level to altitude, the emphasis will be on the placebo to caffeine comparisons within each phase at rest (just prior to exercise), at ten minutes of sustained exercise, and at exhaustion.

At sea level, there was little change in mean endurance time to exhaustion with caffeine (26.5 min to 27.5 min; Figure 2). During acute altitude exposure, mean endurance time increased 54% with caffeine treatment relative to the placebo treatment (22.8 min vs 35.0 min; $p<0.01$) with all eight of the subjects improving their times. However, there was a large intersubject variation in the improvements ranging from 9% to 127% (or 2.5 min to 29.5 min). During the third week of continued exposure, mean endurance time was increased 24% with caffeine treatment, approaching statistical significance (30.8 min vs 38.5 min; $0.10< p <0.15$). There continued to be a wide variation between individuals in improvements in endurance time in response to caffeine, although those who improved most with caffeine during the acute phase also tended to improve during the chronic phase ($r=.66$; $0.05 < p < 0.10$). Three individuals did not improve during caffeine treatment at Pikes Peak.

Oxygen Uptakes During Rest, 10 min Exercise, and at Exhaustion

At sea level, resting oxygen uptakes did not differ between treatments (415 ± 31 vs 411 ± 28 ml/min). Likewise, oxygen uptakes measured in the last

minute prior to exhaustion did not differ between treatments (3201 ± 151 vs 3230 ± 145 ml/min). Conversely, significant increases in oxygen uptakes were determined during caffeine treatment after 10 minutes of exercise (3159 ± 158 to 3324 ± 169 ml/min; $p<0.01$).

During the acute phase, the oxygen consumptions were higher during caffeine treatment at rest (421 ± 17 vs 460 ± 24 ml/min; $p<0.03$) and at exhaustion (2387 ± 156 vs 2526 ± 148 ml/min; $p<0.03$). No difference between the two treatments was observed at 10 min of exercise (2288 ± 146 vs 2268 ± 141 ml/min).

Oxygen uptakes determined at rest, after 10 min, and at exhaustion did not differ between treatments during the chronic phase of the altitude exposure.

Ventilation

Resting ventilations did not differ between treatments at rest and at exhaustion during the sea level phase (Figure 3 and Table 1). Ventilations after 10 min of exercise were increased during caffeine treatment (111.0 l/min to 122.0 l/min; $p<0.02$) and were due to increases in tidal volumes (2.49 l/br to 2.75 l/br; $p<0.01$). Differences in breathing frequencies and tidal volumes between treatments were not apparent at any of the other times at sea level.

During the acute phase, ventilations at rest and at exhaustion were higher during caffeine treatment (15.1 l/min to 17.3 l/min and 123.0 l/min to 140 l/min; $p<0.03$). There were no differences in ventilation after 10 min of exercise. While breathing frequencies were not altered with caffeine during the acute phase, tidal volumes did increase at rest (.90 to 1.09 l/min; $0.05< p <0.10$), after 10 min exercise (2.34 to 2.52 l/min; $p< 0.03$), and at exhaustion (2.17 to 2.52 l/min; <0.01). The increase in tidal volume at 10 min exercise

was mathematically "offset" by a small reduction in breathing frequency (from 47 to 43 br/min; $p>0.12$).

During the chronic exposure, ventilations at rest, at 10 min of exercise, and at exhaustion did not differ between treatments. On the other hand, tidal volumes were higher at rest and after 10 min exercise but were offset mathematically by small, nonsignificant reductions in breathing frequencies (Table 1).

End-tidal O_2 increased and end-tidal CO_2 decreased progressively from rest to exercise in each phase ($p<0.01$). However, there were no differences between treatments at rest, 10 minutes exercise, or at exhaustion.

Respiratory exercise ratios were little altered between treatments in each phase. The values were, however, always greater than 1.00 (range:1.022 to 1.122) during exercise indicative of the hyperventilation associated with the high rate of exercise intensity performed by the test subjects.

Heart rate, Stroke Volume, and Cardiac Output

Heart rates during caffeine treatment at sea level increased at rest (68 to 73 b/min;$p<.05$) and after 10 min of exercise (176 to 181 b/min; $p<0.02$). There was no difference at exhaustion between treatments (185 vs 185 b/min).

During the acute exposure, heart rates at rest and after 10 min of exercise were not altered during caffeine treatment (77 vs 77 b/min; 166 vs 167 b/min). There was however, an increase in heart rates during caffeine treatment at exhaustion (170 vs 177 b/min; $p<0.01$).

Similarly, there were no increases in heart rates at rest and after 10 min of exercise during caffeine treatment during the chronic exposure (90 vs 90 b/min; 160 vs 161 b/min). An increase in heart rate at exhaustion was measured during the chronic exposure during caffeine treatment (173 vs 177 b/min; $p<0.01$).

Cardiac outputs measured after 10 min of exercise did not differ between treatments during any of the three phases (Figure 4). Mean cardiac output during the acute phase was approximately 8 l/min higher than the values determined at sea level and during chronic exposure and was due to a large increase in stroke volume (from approximately 115 ml/b at sea level to 174 ml/b during the acute exposure).

Blood Parameters

Free Fatty Acids (Figure 5)

At sea level, during caffeine treatment, free fatty acid concentrations tended to be higher at rest, during 10 min of exercise, and at exhaustion. However, because of the large intersubject variability there were no significant differences between treatments at each of the times the free fatty acids were compared.

During the acute and chronic phases, resting concentrations were greatly increased during caffeine treatment and continued to be elevated at 10 min of exercise and at exhaustion.

Plasma Glucose (Figure 6)

At sea level, plasma glucose tended to be higher during caffeine treatment. At 10 min of exercise, plasma glucose was significantly higher during caffeine treatment (96 vs 100 mg%; $p<0.01$).

During the acute exposure, the concentration of plasma glucose was significantly elevated at rest (90 vs 110 mg%; $p<0.01$), at 10 min of exercise (97 vs 108 mg%; $p<0.01$), and at exhaustion (109 vs 124 mg%; $p<0.05$) during caffeine treatment.

At Pikes Peak, plasma glucose tended to be elevated during caffeine treatment; with the differences reaching statistical significance at 10 min of exercise (95 vs 101 mg%; $p<0.01$) and at exhaustion (102 vs 115 mg%; $p<0.02$).

Plasma Lactate (Figure 7)

At sea level and during the acute altitude exposure, plasma concentrations of lactate were little altered during caffeine treatment, although resting concentrations were statistically higher ($p<0.04$).

During the chronic exposure, lactate concentration was higher during caffeine treatment at exhaustion (5.63 vs 6.41 mM; $p<0.03$).

Ratings of Perceived Exertion (RPE) (Figure 8)

During all three phases, the values for local, central, and overall ratings of RPE at 10 min of exercise tended to be lower during caffeine treatment. However, only during the acute altitude phase were all three of the ratings significantly lower; local rating decreased from 15.5 to 13.5 ($p<0.05$), central rating decreased from 14.8 to 13.1 ($p<0.05$), and overall from 15.0 to 13.5 ($p<0.05$). At sea level, only the central rating was statistically lower with caffeine treatment (15.3 to 13.6; $p<0.05$). During chronic exposure to altitude, the RPE values were reduced, though not significantly ($0.05 < p < 0.10$).

Caloric Intake and Composition

The total caloric intake and composition (percentages of carbohydrate, fat and protein) did not differ between the three phases (sea level, acute and chronic altitude exposure) as shown in Figure 9.

III. DISCUSSION:

It is well established that exposure to altitude affects a multitude of physiological processes which include and transcend the ventilatory, cardiovascular, and metabolic systems (12,26). The magnitudes of the induced changes caused by acute altitude exposure are altered as the exposure continues from hours to days to weeks (26). Coupled with these dynamic changes are wide interindividual differences (12).

Submaximal endurance time to exhaustion also has a large interindividual variablity; different individuals exercising at the same relative exercise intensity will vary widely in the amount of time to reach their exhaustion endpoints (1). Differences in training status, diet, and "mental toughness" are but a few of the factors which have been determined to have a profound effect on endurance times (1,6).

There are also large interindividual differences in the tolerance, metabolism, excretion and bodily distribution of caffeine (19). Habitual caffeine users become desensitized or develop a tolerance to caffeine that is evident at rest and during exercise (10). Conversely, caffeine-naive individuals, or habitual caffeine users who abstain from caffeine for a few days have been shown to have a potentiated response as evidenced by increases in oxygen consumption and in plasma levels of free fatty acids and norepinephrine at rest and/or during exercise (2,10).

The current study was designed with all of these potentially confounding factors in mind. The investigators, equipment, and cycling protocol were identical throughout the study. Temperature and humidity were similar at each locality. The treatment sequence within each phase was randomly chosen and balanced. The same test subjects were used in each phase and for both treatments within each phase to minimize interindividual variations due to

altitude exposure, endurance times to exhaustion, and caffeine tolerances. Individual exercise intensities within each phase were closely matched between treatments to eliminate the possibility that differences in endurance times would result from differences in exercise intensities.

The daily sequence and composition of the meals from phase to phase were identical to minimize the effects of diet on endurance performance (1,6,23). The diet was devoid of all caffeine (with the exception of the caffeine cocktail). All subjects on all testing days finished eating their meal and drinking their placebo or caffeine cocktail two hours and one hour, respectively, prior to initiating the endurance tests in an effort to eliminate differences in endurance times due to differences in plasma levels of fuels and caffeine.

It was decided to maintain the order of exercise testing on each day to insure that diurnal variations could not be accountable for any changes in endurance times measured. The treatment sequence within each of the three phases also was rigidly adhered to so that consistencies in the number of days on the diet prior to each treatment and the number of days of rest between treatments for each subject could be maintained.

After controlling for all the above factors, it was determined that caffeine had a profound effect on endurance time to exhaustion at altitude despite having no effect at sea level. While it is clear that caffeine affected a multitude of physiological processes both at rest and during exercise, it is not clear what the mechanism(s) was which caused the improvement in endurance performance at altitude to occur. However, since the physiological alterations attributed to caffeine treatment were similar between phases, the improvement in endurance time to exhaustion at altitude must have been due to something beneficial at altitude but not sea level.

A number of studies which have utilized trained cyclists or runners and/or less intense exercise intensities (e.g., 70% VO_{2max}) have shown that endurance performance is enhanced at sea level after caffeine ingestion (8,10,14). In each of these studies, the improvement was at least partially attributed to an increase in fatty acid mobilization and utilization which, in turn, spared muscle glycogen. However, it is important to emphasize that mean endurance times in these prior studies were an hour or more in duration before and after caffeine treatment.

In the present investigation, more severe exercise intensities (79 to 85% V02max) were used by noncyclists resulting in shorter endurance times to exhaustion (mean: 31 min). In this scenerio, increases in plasma free fatty acid mobilization and utilization due to caffeine ingestion would not be expected to be as beneficial since it is not likely that glycogen stores would be depleted (6,25,26). Our data show that there was no evidence of hypoglycemia typically observed at exhaustion after longer endurance bouts (Figure 6) indicating that liver and muscle stores of glycogen were indeed not depleted at exhaustion. Furthermore, a previous study by our laboratory has shown that post-exercise muscle glycogen stores (via muscle biopsies) are no more than 50% depleted after 30 minutes at 80% V02max at sea level and 4300 m altitude (25). The high levels of lactate measured in each phase, independent of treatment (Figure 7), would suggest that failure to continue pedalling, which occurred in less than an hour in all but one test (out of 48), was due to an accumulation of metabolic by-products (6).

If exhaustion can not be attributed to muscle glycogen depletion, then sparing of muscle glycogen usage would not be expected to postpone exhaustion and increase endurance times during caffeine treatment. Thus, it appears that the caffeine-induced increases in plasma FFA measured in the present study can not be implicated as the reason endurance time to exhaustion was enhanced at

altitude. However, the fact that endurance time to exhaustion was improved during caffeine treatment at altitude and not sea level suggests that some physiological variable(s) gains in importance with altitude exposure.

The heart rate response to caffeine treatment was inconsistent between phases. At sea level, significant increases in heart rate were measured at rest and after 10 min of exercise, but not at exhaustion. At altitude, increases in heart rate were measured during caffeine treatment at exhaustion only. However, the increases in heart rate are of questionable physiological importance when it is considered that cardiac outputs during exercise were not altered between treatments in any of the phases. In other words, the increase in endurance performance at altitude during caffeine treatment could not be attributed to an increase in oxygen transport secondary to a cardiovascular enhancement.

Ratings of perceived exertion were measured because it has been shown repeatedly that caffeine causes a reduction in the sensation of fatigue during endurance exercise which has been thought to be at least partially responsible for the improvement in endurance times (3,8,14). In the present study, the perception of effort during cycling tended to be reduced during treatment with caffeine in all three phases for each of the differentiated ratings (local, central, and overall). However, while the magnitudes of the reductions were similar between treatments in each of the phases, the magnitude of improvement in endurance time to exhaustion varied from no improvement at sea level, to a 54% improvement during the acute exposure, to a 24% improvement during chronic exposure. These data would seem to suggest that a reduction in the perception of effort is caused by caffeine, as has been commonly reported (3,8,14,19), but that the reduction is probably not related to the increases in endurance time measured at altitude.

Dietary or cardiovascular alterations also could not account for the improvement in ETX at altitude in the present study. Furthermore, because each subject served as his own control between treatments as well as between phases, it is not likely that the improvement in ETX at altitude was related to the reported positive ergogenic effect of caffeine on human skeletal muscle (16). If a positive ergogenic effect on skeletal muscle was responsible for improving ETX, then the improvement would have occurred at sea level as well.

The above findings indicated that the improvement in ETX at altitude was not associated with caffeine-induced changes in substrate mobilization and utilization, or a reduction in perceived exertion. This conclusion is similar to the only other investigation known to study the effects of caffeine at altitude. Berglund and Hemmingsson (3) studied the effect of caffeine (6 mg/kg) on exercise time over a 21-km distance in 14 well-trained cross-country skiers at 300 m and 2900 m altitude. At the lower altitude there was a small, non-statistically significant reduction in exercise time during caffeine treatment. At the higher altitude the exercise time during caffeine treatment was reduced by 3.2% ($p<0.001$). Because of the relatively short mean exercise times (59 min and 78 min at the low and higher altitude, respectively), the authors concluded that it was unlikely that the improved times during caffeine treatment were due to a delay in glycogen depletion. However, they had no other explanation for the improvement.

Caffeine has been shown to be a respiratory stimulant (20). The exact mechanism(s) for the increase in ventilation are not clear (19), although several have been proposed including: direct stimulation of the respiratory medullary complex; an increase in the central chemosensitivity to CO_2; and an effect on the inputs from the peripheral chemoreceptors (22).

In the present study tidal volumes, but not breathing frequencies, were increased during exercise in each of the phases during caffeine treatment.

This ventilatory effect of caffeine could explain the seemingly paradoxical observation of a lack of improvement in ETX at sea level and a profound improvement in ETX at altitude. An increase in tidal volume reduces the O_2 gradient between the environment and alveolar air, and increases the O_2 pressure to the capillary blood (15). At sea level, where O_2 saturation is already high during rest and exercise (>97%) there is little advantage to be gained by increasing tidal volume. Thus an increase in alveolar O_2 pressure secondary to an increase in tidal volume would not be expected, and was not determined, to be beneficial in increasing ETX at sea level.

During acute exposures to 4300 m altitude, O_2 saturations at rest and exercise have been shown to be reduced to approximately 84% and 75%, respectively, under similar experimental conditions (12,18). An increase in tidal volume at altitude would be beneficial by causing O_2 saturation to be higher than it otherwise would be, thereby enhancing O_2 transport. Tidal volumes during exercise increased in all eight of our test subjects and all eight had improvements in ETX during caffeine treatment (mean: 54%).

As altitude exposure (4300 m) continues to two to three weeks, arterial O_2 saturation at rest and during exercise improves to approximately to 88% and 85%, respectively, due to hypoxia-induced ventilatory adaptations (18,26). This increase in saturation, by itself, would tend to lessen the benefit of a given increase in tidal volume. However, the magnitude of the caffeine-induced increase in tidal volume also was reduced during the chronic phase. The impact of both of these changes apparently lessened, but did not eliminate, the salutatory effect of caffeine on endurance time to exhaustion since endurance times still improved by 24%.

While arterial saturations were not measured in the present investigation, our conclusions are consistent with the findings of Berglund and Hemmingsson (3). In their study, caffeine had little effect on exercise

time at 300 meters altitude where arterial saturation is little altered from sea-level values. However, at 2900 meters where arterial saturation would be lower (~ 90%) there was a significant improvement in race times during caffeine treatment.

IV. SUMMARY:

Submaximal ETX was not altered during caffeine treatment at sea level but was improved by 54% and 24% after 1 hour and three weeks at altitude, respectively. The improvements in ETX were determined not to be associated with substrate mobilization and use, or a reduction in the perception of effort. Dietary or cardiac output changes also could not account for the improvements. However, increases in tidal volume during caffeine administration suggest that the improvement in ETX at altitude may be related to an increase tidal volume which increases the partial pressure of alveolar O_2 and enhances arterial saturation and oxygen transport.

V. REFERENCES:

1. Astrand PO, Rodahl K. Textbook of Work Physiology, New York:McGraw-Hill Book Co., 1986.

2. Bellet S, Kershbaum A, Finck EM. Response of free fatty acids to coffee and caffeine. Metabolism 1968;17:702-707.

3. Berglund B, Hemmingsson P. Effects of caffeine ingestion on exercise performance at low and high altitudes in cross-country skiers. Int. J. Sports Med. 1982; 3:234-236.

4. Borg GAV. Perceived exertion: a note on "history" and methods. Med. Sci. Sports 5(2):90-93, 1973.

5. Cadarette B. Effects of varied doses of caffeine on endurance exercise to fatigue. Masters Thesis, Boston University (Sargent College), 1982

6. Costill DL. Carbohydrates for exercise: Dietary demands for optimal performance. Int. J. Sports Med. 1988;9:1-18.

7. Costill DL, Coyle E, Dalsky G, Evans W, Fink W, Hoopes D. Effects of elevated plasma FFA and insulin on muscle glycogen usage during exercise. J. Appl. Physiol. 1977;43:695-699.

8. Costill DL, Dalsky GP, Fink WJ. Effects of caffeine ingestion on metabolism and exercise performance. Med. Sci. Sports. 1978; 10:155-158.

9. Essig D, Costill DL, Van Handel PJ. Effects of caffeine ingestion on utilization of muscle glycogen and lipid during leg ergometer cycling. Int. J. Sports Med. 1980;1:86-90.

10. Fisher SM, McMurray RG, Berry M, Mar MH, Forsythe WA. Influence of caffeine on exercise performance in habitual caffeine users. Int. J. Sports Med. 1986; 7:276-280.

11. Fulco CS. Human acclimatization and physical performance at high altitude. J. Appl. Sport Science Res. 2(4):79-84, 1988.

12. Fulco CS, Cymerman A. Human performance and acute hypoxia. In:Human Performance Physiology and Environmental Medicine at Terrestrial Extremes. Pandolf KB, Sawka MN, Gonzalez RR. (Ed.) Indianapolis, IN: Benchmark Press. 1988;Chap 12.

13. Horstman D, Weiskopf R, Jackson RF. Work capacity during 3-wk sojourn at 4,300 m: Effects of relative polycythemia. J. Appl. Physiol. 1980;49:311-318.

14. Ivy JL, Costill DL, Fink WJ, Lower RW. Influence of caffeine and carbohydrate feedings on endurance performance. Med. Sci. Sports. 1979; 11:6-11.

15. Lenfant C, Sullivan K. Adaptation to high altitude. N. Eng. J. Med. 1971; 284:1298-1309.

16. Lopes JM, Aubier M, Jardim J, Aranda JV, Macklem PT. Effect of caffeine on skeletal muscle function before and after fatigue. J. Appl. Physiol. 1983;54:1303-1305.

17. Maher JT, Jones LG, Hartley H. Effects of high-altitude exposure on submaximal endurance capacity of men. J. Appl. Physiol. 1974;37:895-898.

18. Moore LG, Cymerman A, Huang S-Y, McCullough RE, McCullough RG, Rock PB Young AJ, Young P, Bloedow, D, Weil JV, Reeves JT. Propranolol does not impair exercise oxygen uptake in normal men at high altitude. J. Appl. Physiol. 1986; 61(5): 1935-1941.

19. Powers SK, Dodd S. Caffeine and endurance performance. Sports Med. 1985; 2:165-174.

20. Powers SK, Dodd S, Woodyard J, Mangum M. Caffeine alters ventilatory and gas exchange kinetics during exercise. Med. Sci. Sports Exerc. 1985; 18:101-106.

21. Technical Bulletin (TB Med 288). Medical problems of man at high terrestrial elevations. Department of the Army. 1975.

22. Trippenbach R, Zinman R, Milic-Emili J. Caffeine's effect on breathing patterns and vagal responses in newborn rabbits. Res. Physio. 1980; 40:211-223.

23. Weir J, Noakes TD, Myburgh K, Adams K. A high carbohydrate diet negates the metabolic effects of caffeine during exercise. Med. Sci. Sports Exerc. 1987; 19:100-107.

24. Young AJ, Cymerman A, Pandolf KB. Differentiated ratings of perceived exertion are ifluenced by high altitude exposure. Med. Sci. Sports Exercise. 1982; 14:223-228.

25. Young AJ, Evans WJ, Cymerman A, Pandolf KB, Knapik JJ, Maher JT. Sparing effect of chronic high-altitude exposure on muscle glycogen utilization J. Appl. Physiol. 1982;52:857-862.

26. Young AJ, Young PM. Human acclimatization to high terrestrial altitude. In:Human Performance Physiology and Environmental Medicine at Terrestrial Extremes. Pandolf KB, Sawka MN, Gonzalez RR. (Ed.) Indianapolis, Benchmark Press. 1988;Chap 13.

TABLE 1

BREATHING FREQUENCY (b/min)

	Rest		10' Exercise		Exhaustion	
	Placebo	Caffeine	Placebo	Caffeine	Placebo	Caffeine
PHASE:						
I	17 ± 1	16 ± 1	45 ± 3	45 ± 2	53 ± 3	53 ± 3
II	17 ± 2	18 ± 2	47 ± 2	43 ± 2	57 ± 2	55 ± 2
III	22 ± 1	23 ± 2	48 ± 2	46 ± 2	58 ± 2	59 ± 2

n = 8; Values are means ± SE

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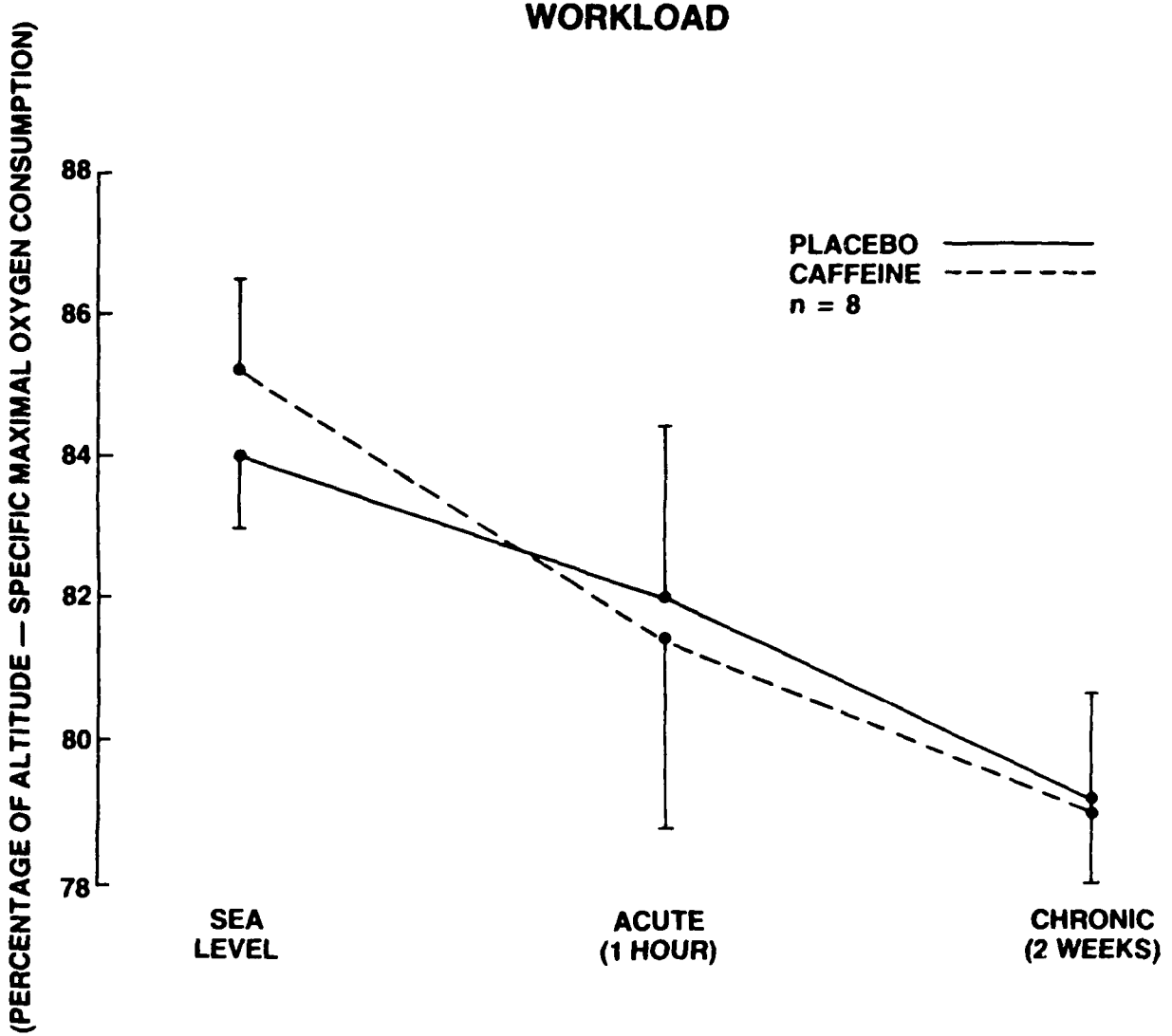
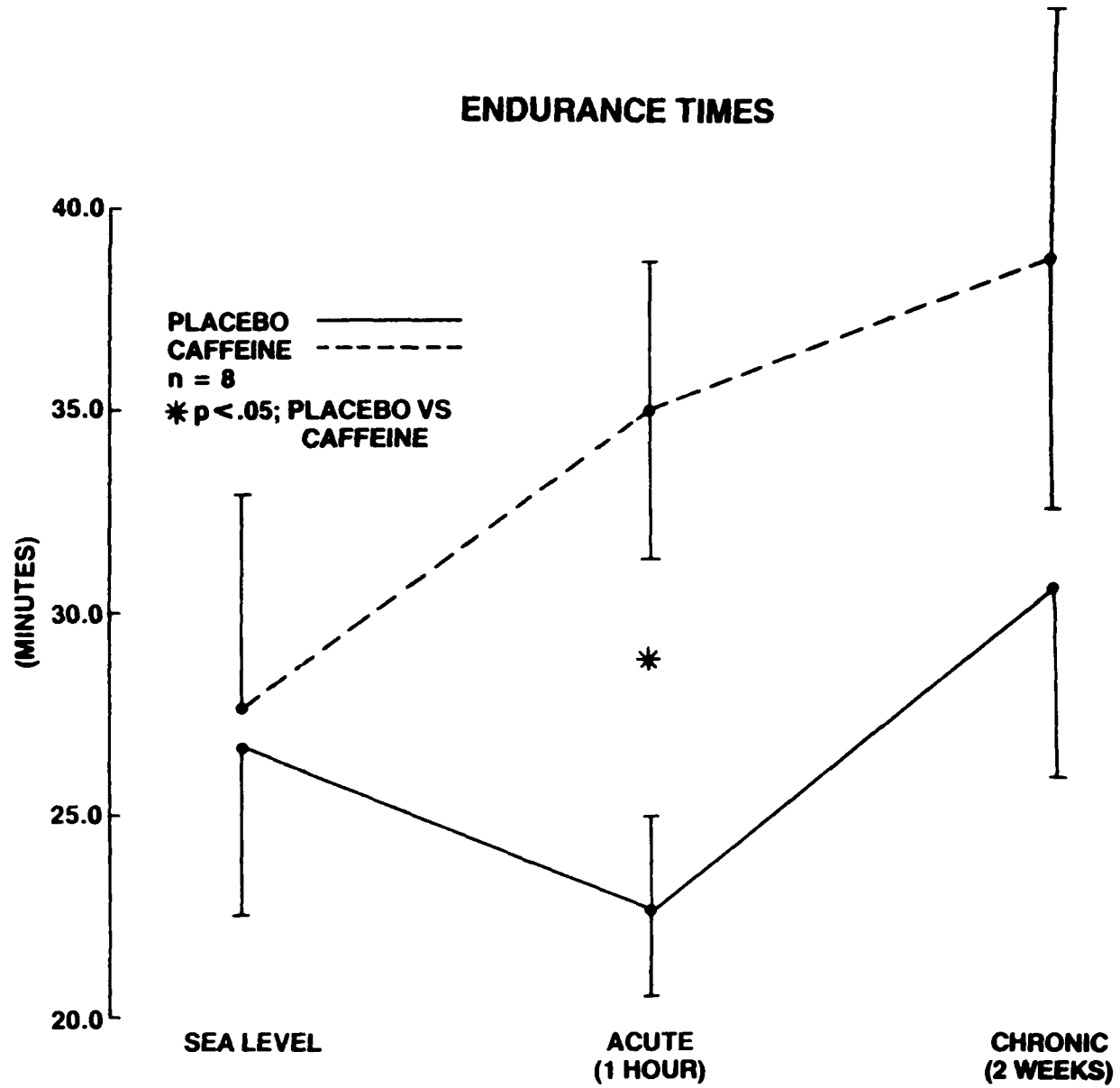
****

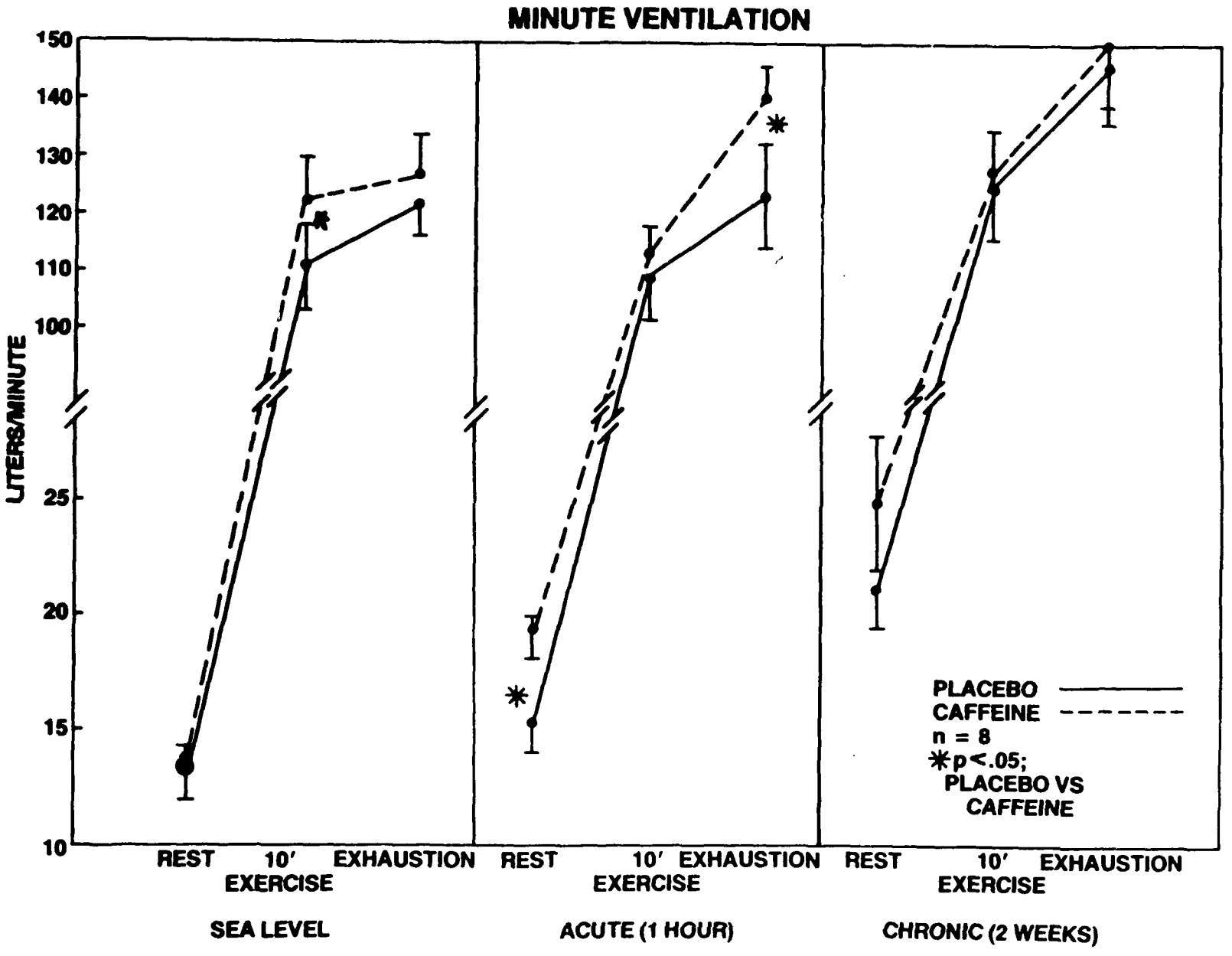
TIDAL VOLUME (ml/br)

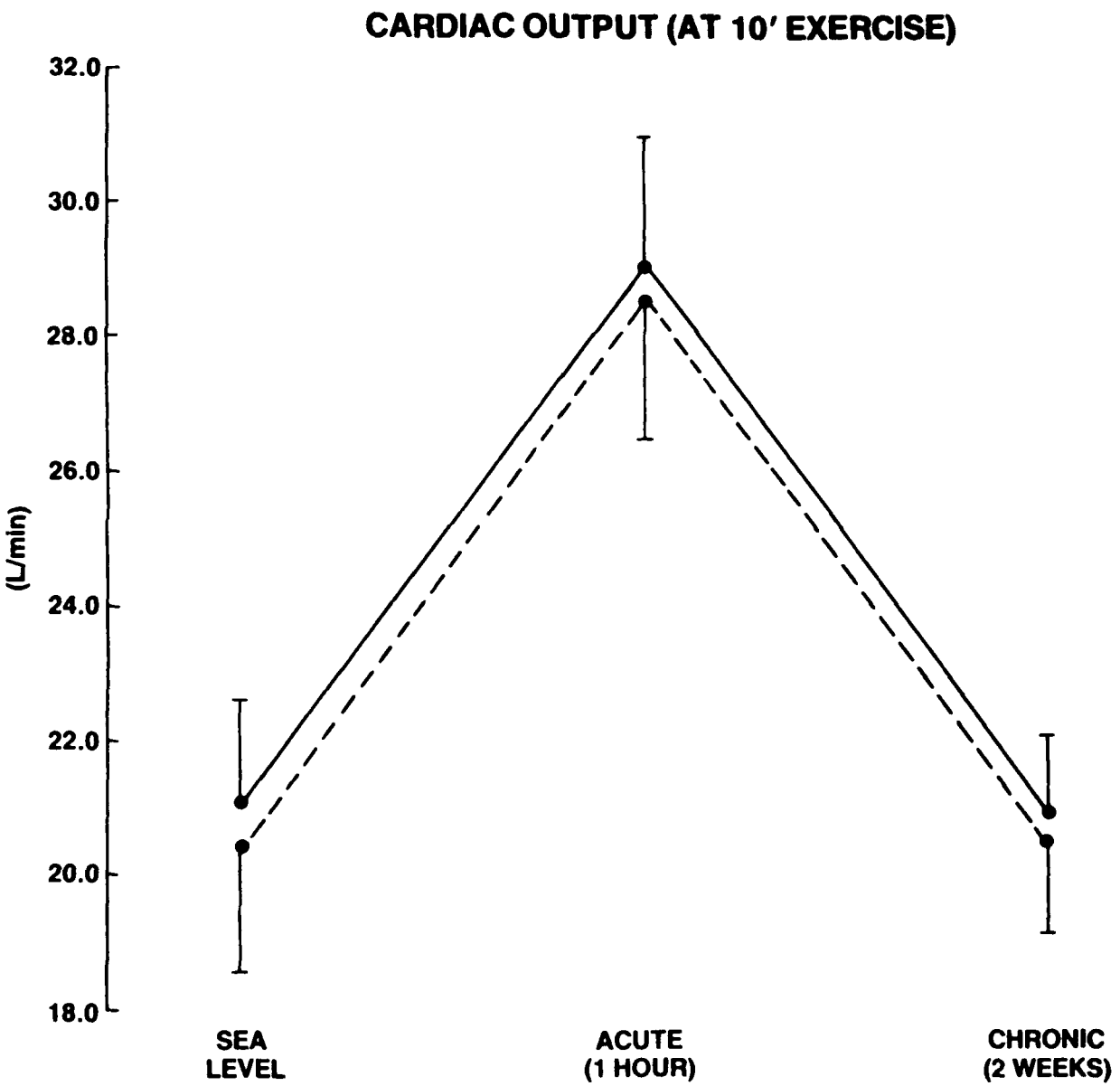
	Rest		10' Exercise		Exhaustion	
	Placebo	Caffeine	Placebo	Caffeine	Placebo	Caffeine
PHASE:						
I	0.86 ± 0.10	0.88 ± 0.06	2.49 ± 0.15 *	2.75 ± 0.15	2.32 ± 0.10	2.39 ± 0.08
II	0.90 ± 0.04	1.09 ± 0.15	2.34 ± 0.15 *	2.52 ± 0.18	2.17 ± 0.16 *	2.52 ± 0.17
III	1.00 ± 0.06 *	1.19 ± 0.13	2.65 ± 0.17 *	2.75 ± 0.18	2.53 ± 0.17	2.57 ± 0.17

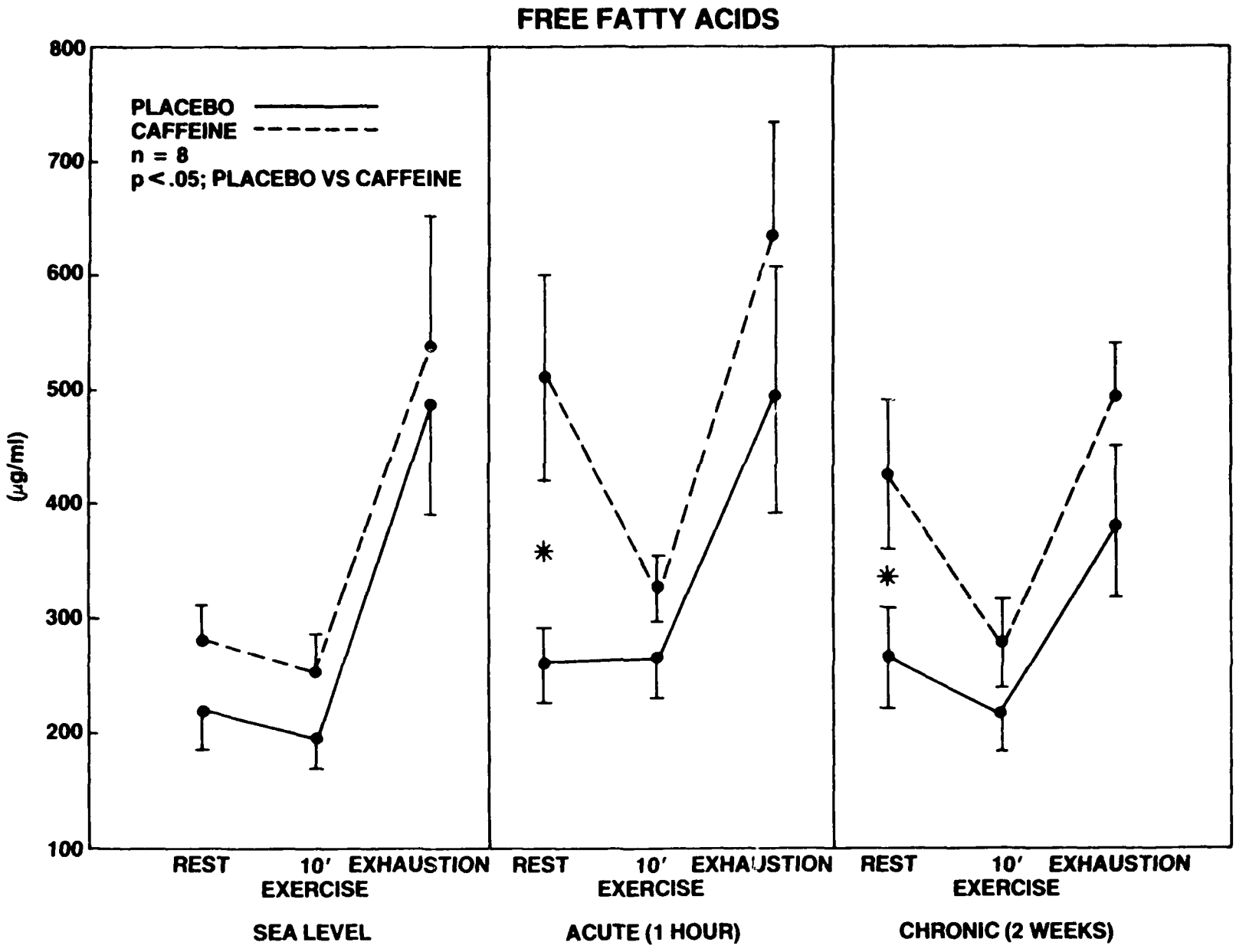
n = 8; Values are means ± SE; *p<0.05

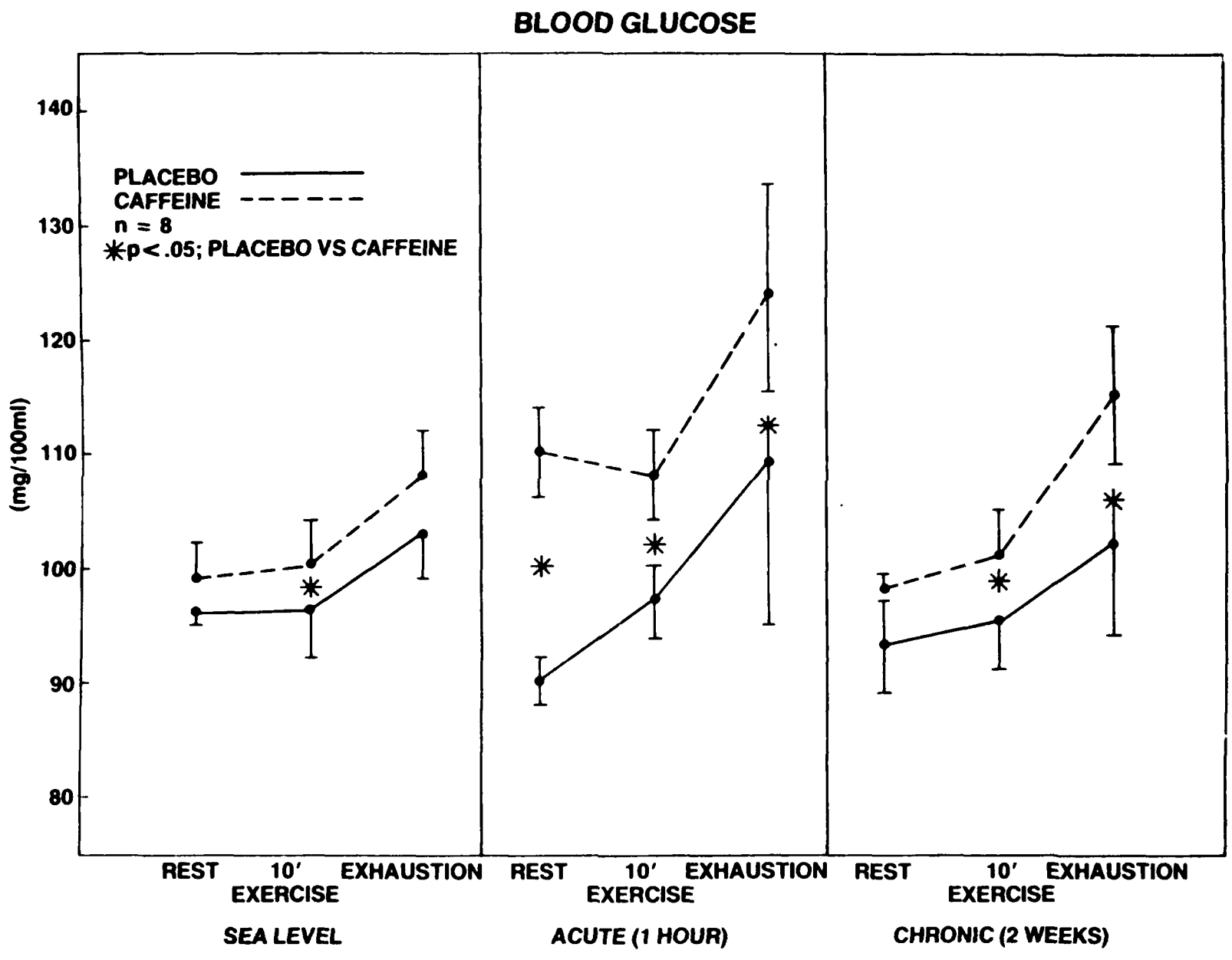

WORKLOAD
(PERCENTAGE OF ALTITUDE — SPECIFIC MAXIMAL OXYGEN CONSUMPTION)
88
86
84
82
80
78
PLACEBO
CAFFEINE
n = 8
SEA LEVEL
ACUTE (1 HOUR)
CHRONIC (2 WEEKS)

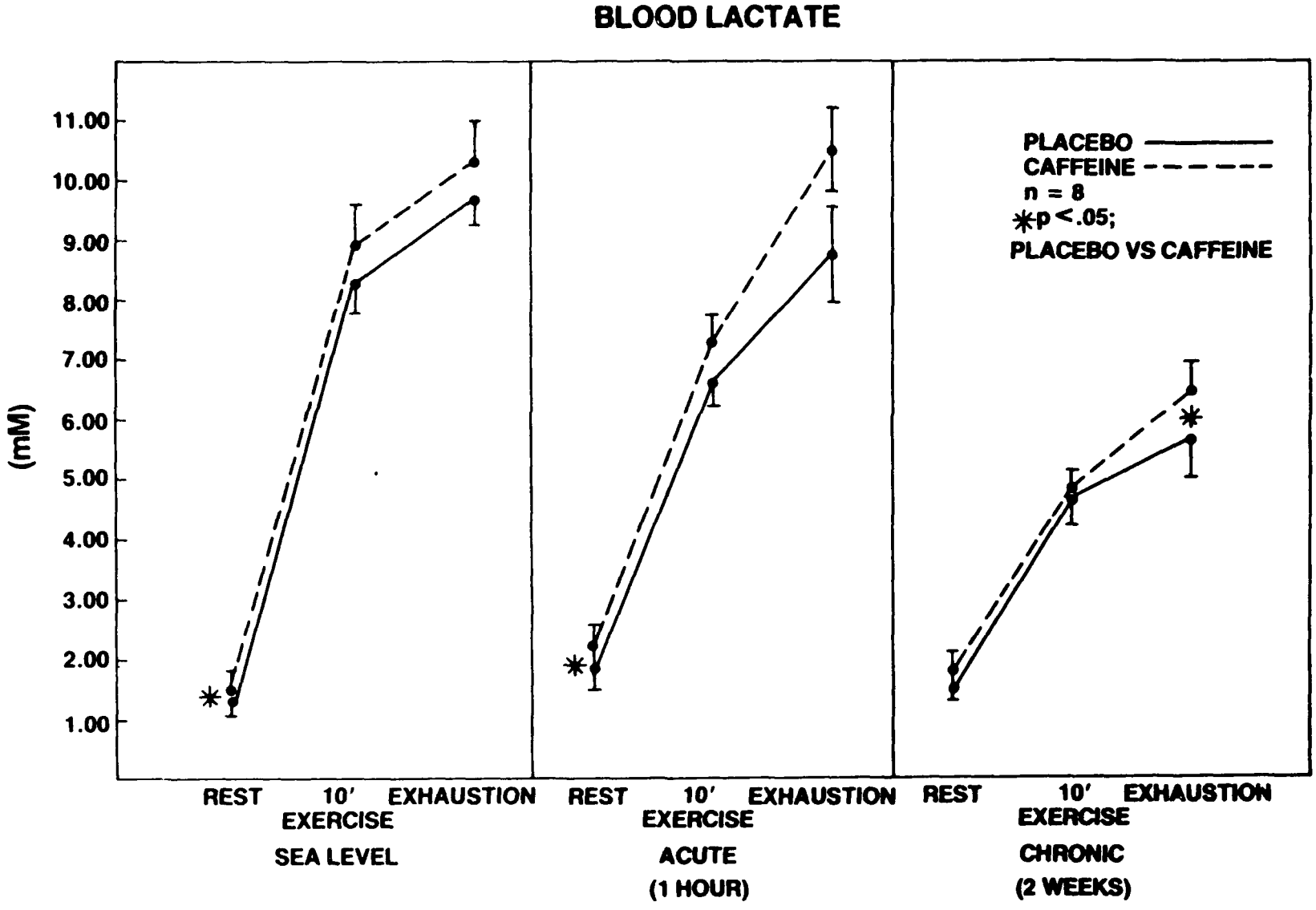

ENDURANCE TIMES
40.0
35.0
30.0
25.0
20.0
(MINUTES)
PLACEBO
CAFFEINE
n = 8
* p < .05; PLACEBO VS CAFFEINE
SEA LEVEL
ACUTE (1 HOUR)
CHRONIC (2 WEEKS)

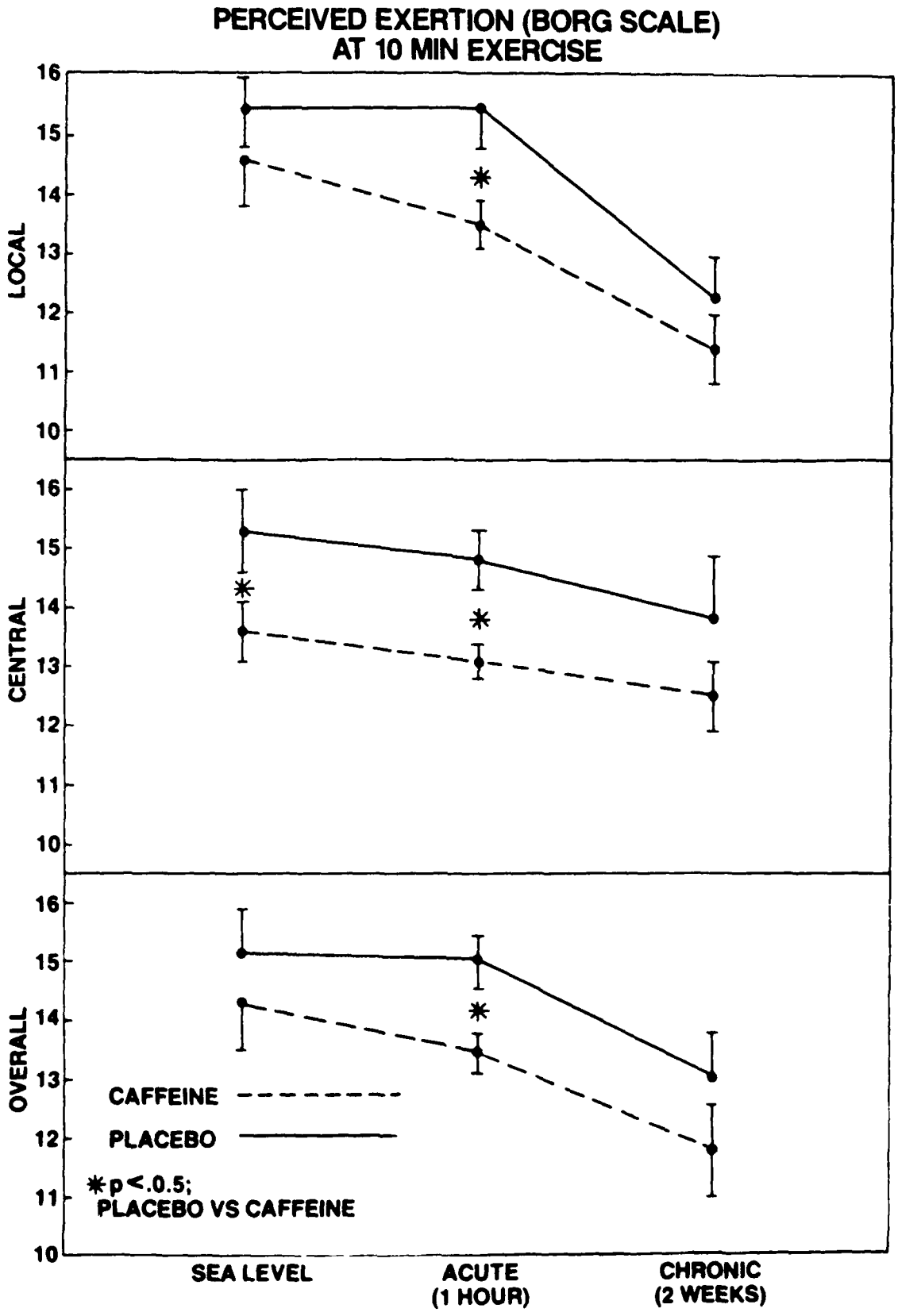

MINUTE VENTILATION
LITERS/MINUTE
150
140
130
120
110
100
25
20
15
10
REST
10'
EXHAUSTION
EXERCISE
SEA LEVEL
ACUTE (1 HOUR)
CHRONIC (2 WEEKS)
PLACEBO
CAFFEINE
n = 8
*p<.05;
PLACEBO VS
CAFFEINE

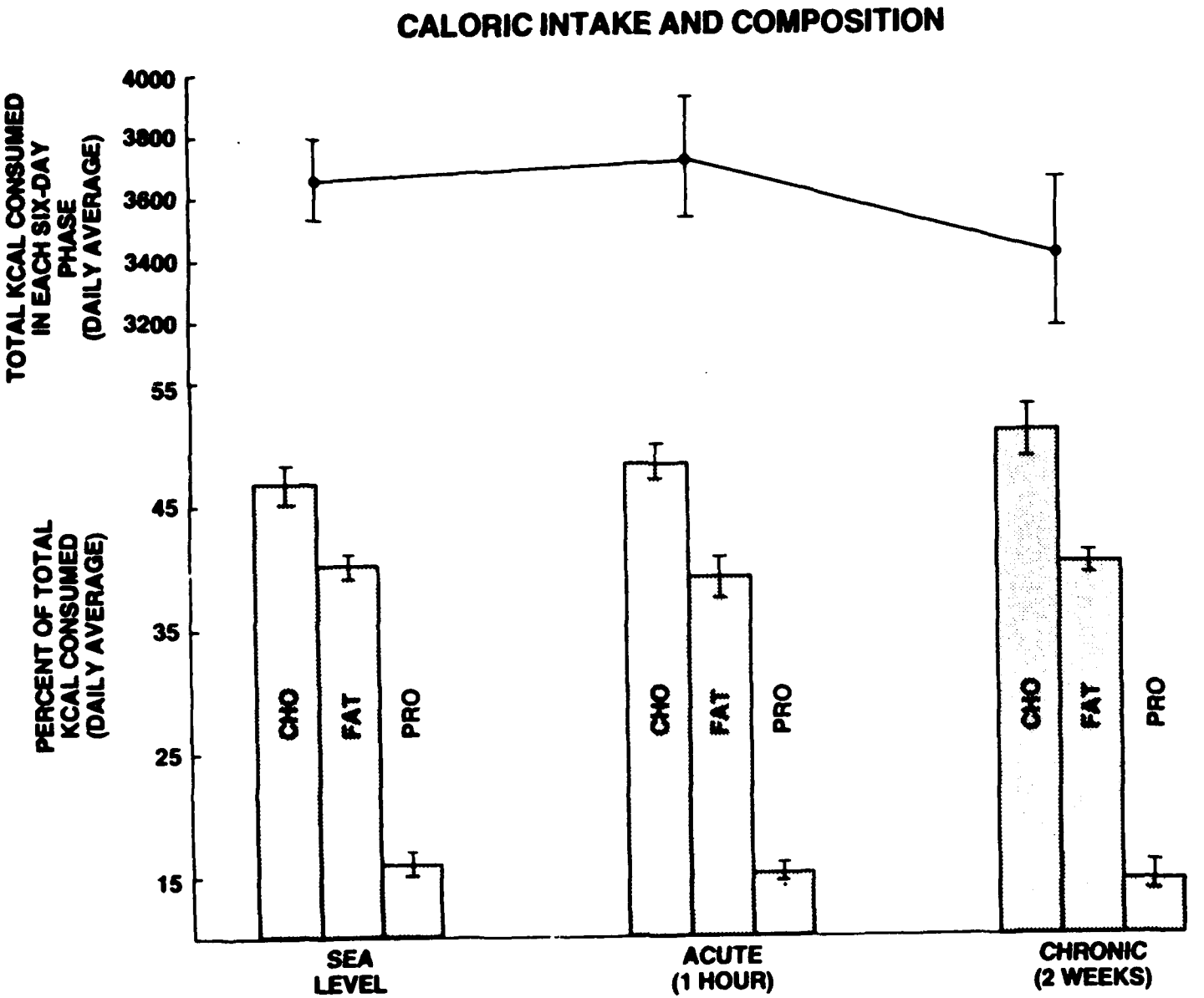

CARDIAC OUTPUT (AT 10′ EXERCISE)
32.0
30.0
28.0
26.0
24.0
22.0
20.0
18.0
(L/min)
SEA LEVEL
ACUTE (1 HOUR)
CHRONIC (2 WEEKS)


FREE FATTY ACIDS
PLACEBO
CAFFEINE
n = 8
p < .05; PLACEBO VS CAFFEINE
800
700
600
500
400
300
200
100
(μg/ml)
REST
10′ EXERCISE
EXHAUSTION
SEA LEVEL
ACUTE (1 HOUR)
CHRONIC (2 WEEKS)


BLOOD GLUCOSE
PLACEBO
CAFFEINE
n = 8
*p < .05; PLACEBO VS CAFFEINE
140
130
120
110
100
90
80
(mg/100ml)
REST
10'
EXHAUSTION
EXERCISE
SEA LEVEL
ACUTE (1 HOUR)
CHRONIC (2 WEEKS)


BLOOD LACTATE
11.00
10.00
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
(mM)
PLACEBO
CAFFEINE
n = 8
*p < .05;
PLACEBO VS CAFFEINE
REST
10'
EXHAUSTION
EXERCISE
SEA LEVEL
REST
10'
EXHAUSTION
EXERCISE
ACUTE
(1 HOUR)
REST
10'
EXHAUSTION
EXERCISE
CHRONIC
(2 WEEKS)


PERCEIVED EXERTION (BORG SCALE)
AT 10 MIN EXERCISE
LOCAL
CENTRAL
OVERALL
16
15
14
13
12
11
10
CAFFEINE
PLACEBO
*p<.0.5;
PLACEBO VS CAFFEINE
SEA LEVEL
ACUTE
(1 HOUR)
CHRONIC
(2 WEEKS)


CALORIC INTAKE AND COMPOSITION
TOTAL KCAL CONSUMED IN EACH SIX-DAY PHASE (DAILY AVERAGE)
4000
3800
3600
3400
3200
55
45
35
25
15
PERCENT OF TOTAL KCAL CONSUMED (DAILY AVERAGE)
CHO
FAT
PRO
CHO
FAT
PRO
CHO
FAT
PRO
SEA LEVEL
ACUTE (1 HOUR)
CHRONIC (2 WEEKS)

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